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Attorney's Docket No.: 07039-170002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Jorg J. Goronzy et al.	Art Unit	: 1648
Serial No.	: 09/723,000	Examiner	: Stacy Brown
Filed	: November 27, 2000		
Title	: METHODS AND MATERIALS FOR EVALUATING RHEUMATOID ARTHRITIS		

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Mayo Foundation for Medical Education and Research.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 1-47, 58, and 59 have been previously cancelled without prejudice.

Claims 48-57 and 60-62 are pending and stand finally rejected.

(4) Status of Amendments

All amendments have been entered.

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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(5) Summary of Invention

The presently claimed invention relates to methods and kits for determining the predisposition of a rheumatoid arthritis patient to develop severe disease by (1) determining the frequency of $CD4^+/CD28^{null}$ cells in the patient and (2) determining the presence or absence of an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele in the patient. *See, e.g.*, page 4, lines 4-13 of Applicants' specification.

(6) Issue

Whether the subject matter of claims 48-57 and 60-62 would have been obvious in view of the Goronzy *et al.* reference (*J. Clin. Investigation, Inc.*, 94:2068-2076 (1994)) combined with the Abril *et al.* reference (*Arthritis Rheum.*, 40:762 (1998))?

(7) Grouping of Claims

Claims 48-57 and 60 stand or fall together.

The remaining claims, claims 61 and 62, are separately patentable and fall into separately patentable groups as follows. Claim 61 stands or falls alone. Claim 62 stands or falls alone.

(8) Argument

Whether the subject matter of claims 48-57 and 60-62 would have been obvious in view of the Goronzy *et al.* reference combined with the Abril *et al.* reference?

A. Grouping of Claims for this Issue

Claims 48-57 and 60 stand or fall together. The remaining rejected claims, claims 61 and 62, fall into separately patentable groups as follows. Claim 61 stands or falls alone, and forms a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should determine the frequency of $CD4^+/CD28^{null}$ cells in a patient and the presence or absence of an HLA-DRB1 allele in the patient does not necessarily anticipate or render obvious a claim reciting a kit containing (1) a first binding pair member having specific binding affinity for

a $CD4^+/CD28^{null}$ cell marker and (2) an oligonucleotide primer having specific binding affinity for at least a portion of the locus containing an HLA-DRB1 allele.

Claim 62 stands or falls alone, and forms a separately patentable claim since any teaching or suggestion that a person having ordinary skill in the art should determine the frequency of $CD4^+/CD28^{null}$ cells in a patient and the presence or absence of an HLA-DRB1 allele in the patient does not necessarily anticipate or render obvious a claim reciting a kit containing (1) a first binding pair member having specific binding affinity for a $CD4^+/CD28^{null}$ cell marker, (2) an oligonucleotide primer having specific binding affinity for at least a portion of the locus containing an HLA-DRB1 allele, and (3) a reference chart containing information about $CD4^+/CD28^{null}$ cell frequencies.

B. Arguments for Reversal of Examiner's Rejection Regarding this Issue

Proper analysis under 35 U.S.C. § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process or make the claimed product, and (2) whether the prior art would also have revealed that in so carrying out or making, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). It is axiomatic that in order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, a prior art reference must teach or suggest, alone or in combination with other prior art references, each and every element of the claimed invention. *See, e.g.*, MPEP § 2143. The Federal Circuit warns that "both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure," and that "it is impermissible to use the claimed invention as a 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *See, In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988) and *In re Fritch*, 972 F.2d 1260 (Fed Cir. 1992).

When determining obviousness, the fact that a reference teaches away from the claimed invention is a significant factor that must be considered. In fact, a "prima facie case of obviousness can be rebutted if the applicant . . . can show that the art in any material respect taught away from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). "A reference may be said to teach away when a person of ordinary skill, upon reading the

reference, . . . would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353 1360 (Fed. Cir. 1999).

In addition, the so-called "secondary" considerations, such as unexpected results, should be considered in every case when present. See, e.g., *In re Sernaker*, 702 F.2d 989 (Fed. Cir. 1983) citing *In re Fielder and Underwood*, 471 F.2d 640 (Cust. & Pat. App. 1973). In fact, the Federal Circuit stated that:

> evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Stratoflex, Inc., v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

1. Claims 48-57 and 60

In the Official Action mailed May 19, 2003, the Examiner stated that the Goronzy *et al.* reference teaches that most patients with Felty's syndrome and patients with other extra-articular rheumatoid organ manifestations have twice as many disease associated HLA-DRB1 alleles. The Examiner also stated that the Abril *et al.* reference teaches that CD28 deficient $CD4^+$ T cells appear to play a critical role in the disease process leading to RA, suggesting that genes controlling the expression of CD28 deficient T cells represent novel disease risk genes in rheumatoid arthritis. After making these statements, the Examiner concluded that:

> one of ordinary skill in the art would have been motivated to use the teachings of Abril in Goronzy's method of analyzing the presence of $CD4^+$ T cells and clonal expansion of T cells. One would have been motivated by Abril's teaching that CD28 deficient cells represent risk genes in RA. One could have had a reasonable expectation of success that the method and materials of Abril would have worked in Goronzy's method because both are looking at $CD4^+$ T cells' role in RA progression. . . . Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

On September 19, 2003, Applicants filed a response pointing out that a person having ordinary skill in the art would have known from Chapman *et al.* (*J. Immunol.*, 157:4771-4780 (1996)) that $CD4^+/CD28^{null}$ cell frequencies are associated with HLA-DRB1 alleles such as

HLA-DRB1 *0401. Thus, assuming one would have been motivated to determine a rheumatoid arthritis patient's predisposition to develop severe disease, one might have assessed either $CD4^+/CD28^{null}$ cell frequencies or HLA-DRB1 alleles, but not both.

In the Advisory Action mailed April 20, 2004, the Examiner stated that the Abril *et al.* reference:

> teaches that CD28null cells suggest that genes controlling their expression represent disease risk genes. This teaching would have motivated one of ordinary skill to test for the presence/absence of Goronzy's alleles. Applicant argues that neither Goronzy nor Abril recognize that the measurements are independent of each other. However, such recognition is not required, since one would have been motivated to use both measurements, as is instantly claimed.

Applicants respectfully disagree. Claims 48-57 and 60, which stand or fall together, recite comparing the frequency of $CD4^+/CD28^{null}$ cells in the patient to a reference frequency to obtain information about the rheumatoid arthritis condition, and determining if the patient is predisposed to develop severe disease based on the information and the presence or absence of a recited HLA-DRB1 allele.

The Chapman *et al.* reference demonstrates that a person having ordinary skill in the art would not have been motivated to combine the cited references as the Examiner has done. In particular, the Chapman *et al.* reference discloses that high $CD4^+/CD28^{null}$ cell frequencies are associated with HLA-DRB1 alleles such as HLA-DRB1 *0401. In other words, as explained in the Chapman *et al.* abstract, "persons with HLA-DRB1 *0401 and DR1 alleles had significantly higher numbers of $CD28^-$ T cells, while individuals with HLA-DR2(15) had significantly fewer $CD28^-CD4^+$ T cells than the mean." A person having ordinary skill in the art reading the Chapman *et al.* reference would have appreciated that the presence of particular HLA-DR alleles in a person means that that person has high or low $CD4^+/CD28^{null}$ cell numbers. Thus, a person having ordinary skill in the art reading the Chapman *et al.* reference together with the cited references would not have been motivated to determine both (a) the presence or absence of a recited HLA-DRB1 allele and (b) the frequency of $CD4^+/CD28^{null}$ cells, as the Examiner contends. Rather, a person having ordinary skill in the art would have simply followed the teachings of the Chapman *et al.* reference to assess a person's HLA alleles or $CD4^+/CD28^{null}$ cell

number, but not both. Given the lack of motivation to combine the cited references as the Examiner has done, it is clear that the presently claimed invention is not obvious.

As explained above, "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353 1360 (Fed. Cir. 1999). And, a "prima facie case of obviousness can be rebutted if the applicant . . . can show that the art in any material respect taught away from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). The Chapman *et al.* reference is such a reference. A person having ordinary skill in the art reading the Chapman *et al.* reference would have been led away from assessing both a person's HLA alleles and $CD4^+/CD28^{null}$ cell numbers since the Chapman *et al.* reference teaches that high $CD28^-CD4^+$ cells numbers are associated with HLA alleles. Thus, the teaching away disclosed in the Chapman *et al.* reference not only rebuts the Examiner's *prima facie* case of obviousness but also demonstrates the non-obviousness of the presently claimed invention. Therefore, the Examiner's rejection under 35 U.S.C. § 103 is improper.

At one point in the Advisory Action mailed April 20, 2004, the Examiner alleged that the authors of the Chapman *et al.* reference teach "measuring both cell frequencies and the presence/absence of HLA-DRB1 alleles." Specifically, the Examiner stated that:

> [a]lthough Chapman does not recognize that the measurements are independent of each other, Chapman performs both measurements, as is instantly claimed. Therefore, while the prior art is silent on the reasoning behind the claimed method, the prior art teaches the claimed method.

This is not correct. The Chapman *et al.* reference discloses the association of $CD28^-CD4^+$ cells with HLA-DR alleles. As explained above, the Chapman *et al.* reference teaches that people with HLA-DRB1 *0401 and DR1 alleles have significantly higher numbers of $CD28^-$ T cells. At no point does the Chapman *et al.* reference teach or suggest determining the predisposition of a rheumatoid arthritis patient to develop severe disease as recited in present claims 48-57 and 60. Thus, the Chapman *et al.* reference does not teach the presently claimed method.

Additional evidence supporting the patentability of the presently claimed invention includes Applicants' unexpected results. At the time Applicants filed, a person having ordinary

skilled in that art would have understood from the Chapman *et al.* reference that high $CD4^+/CD28^{null}$ cell numbers are associated with HLA-DR alleles. Applicants unexpectedly found that $CD4^+/CD28^{null}$ T cell counts are independent of HLA-DRB1 genotypes when determining a patient's predisposition to develop severe disease. *See*, page 43, lines 24-25 of Applicants' specification. From the Chapman *et al.* reference, one would have expected $CD4^+/CD28^{null}$ T cell counts to be dependent upon HLA-DRB1 genotypes. Applicants' unexpected results provide additional evidence of the non-obviousness of the presently claimed invention.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 48-57 and 60 under 35 U.S.C. § 103.

2. Claim 61

Claim 61, which stands or falls alone, recites a kit containing (1) a first binding pair member having specific binding affinity for a $CD4^+/CD28^{null}$ cell marker and (2) an oligonucleotide primer having specific binding affinity for at least a portion of the locus containing an HLA-DRB1 allele. The Examiner has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the art must teach or suggest all limitations of the claim at issue. *See, e.g.*, MPEP § 2143.03. Neither the Goronzy *et al.* reference nor the Abril *et al.* reference discloses a binding pair member having specific binding affinity for a $CD4^+/CD28^{null}$ cell marker. Thus, the obviousness rejection is improper.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 61 under 35 U.S.C. § 103.

3. Claim 62

Claim 62, which stands or falls alone, recites a kit containing (1) a first binding pair member having specific binding affinity for a $CD4^+/CD28^{null}$ cell marker, (2) an oligonucleotide primer having specific binding affinity for at least a portion of the locus containing an HLA-DRB1 allele, and (3) a reference chart containing information about $CD4^+/CD28^{null}$ cell frequencies. The Examiner has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the art must teach or suggest all limitations of the claim at issue.

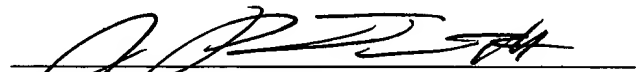
See, e.g., MPEP § 2143.03. Neither the Goronzy *et al.* reference nor the Abril *et al.* reference discloses a binding pair member having specific binding affinity for a $CD4^{+}/CD28^{null}$ cell marker. In addition, at no point do the cited references disclose a reference chart containing information about $CD4^{+}/CD28^{null}$ cell frequencies. Thus, the obviousness rejection is improper.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claim 62 under 35 U.S.C. § 103.

The brief fee of $165 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: July 19, 2004



J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

Appendix of Claims

48. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) comparing the frequency of $CD4^+/CD28^{null}$ cells in said patient to a reference frequency to obtain information about said rheumatoid arthritis condition, and

b) determining if said patient is predisposed to develop severe disease based on said information and the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele.

49. The method of claim 48, wherein said frequency of $CD4^+/CD28^{null}$ cells comprises the percent of $CD4^+$ cells that are CD28 negative.

50. The method of claim 48, wherein said reference frequency is derived from the $CD4^+/CD28^{null}$ cell frequency from a population.

51. The method of claim 50, wherein said population comprises a population of patients having a diffuse rheumatoid arthritis condition.

52. The method of claim 50, wherein said population comprises a population of patients having a follicular rheumatoid arthritis condition.

53. The method of claim 50, wherein said population comprises a population of patients having a granulomatous rheumatoid arthritis condition.

54. The method of claim 50, wherein said population comprises a population of healthy individuals.

55. The method of claim 50, wherein said population comprises a population of patients having subcutaneous nodules.

56. The method of claim 50, wherein said population comprises a population of patients having extra-articular involvement.

57. The method of claim 50, wherein said population comprises a population of patients having major joint destruction.

60. A method for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said method comprising:

a) determining the frequency of $CD4^{+}/CD28^{null}$ cells in said patient,

b) determining the presence or absence of an HLA-DRB1 allele in said patient, wherein said HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele,

c) comparing said frequency of $CD4^{+}/CD28^{null}$ cells to a reference frequency to obtain information about said rheumatoid arthritis condition, and

d) determining if said patient is predisposed to develop severe disease based on said information and said presence or absence of said HLA-DRB1 allele.

61. A kit for determining the predisposition of a rheumatoid arthritis patient to develop severe disease, said kit comprising:

a) a first binding pair member, wherein said first binding pair member has specific binding affinity for a $CD4^{+}/CD28^{null}$ cell marker such that the frequency of $CD4^{+}/CD28^{null}$ cells in said patient is determinable, and

b) an oligonucleotide primer, wherein said oligonucleotide primer has specific binding affinity for at least a portion of the locus containing an HLA-DRB1 allele such that the presence or absence of an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele in said patient is determinable.

62. The kit of claim 61, wherein said kit comprises a reference chart, wherein said reference chart contains information about $CD4^{+}/CD28^{null}$ cell frequencies such that said predisposition is determinable based on said frequency of $CD4^{+}/CD28^{null}$ cells in said patient and said presence or absence of said HLA-DRB1 *0401 allele, said HLA-DRB1 *0404 allele, said HLA-DRB1 *0405 allele, or said HLA-DRB1 *0408 allele.